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DUPONT HASKELL GLOBAL CENTERS FOR HEALTH & ENVIRONMENTAL
SCIENCES
Discovery Toxicology Group

Repeated Dose Oral Toxicity 7-Day Gavage Study in Rats

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STUDY DIRECTOR: Diane L. Nabb, Staff Toxicologist
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OBJECTIVE

To evaluate potential subacute toxicity and kinetic behavior of the test substance when administered by oral gavage to male and female rats for 7 consecutive days.

STUDY DESIGN

Test Substance: HFPO Dimer Acid Ammonium Salt
Lot/Batch Number: E1131181-6
Purity: 86.6% (doses were corrected for purity)
Species: Rat
Strain: CrI:CD(SD)
Gender: Male and Female
Age at start: ~6 weeks
Group Size: Control 5 males, 5 females
Low dose 8 males, 8 females (5/sex Main study, 3/sex Metabolism)
Mid dose 5 males, 5 females (5/sex Main study)
High dose 5 males, 5 females (5/sex Main study)
Dose Levels: 0, 30, 300, 1000 mg/kg Main study
30 mg/kg for Metabolism animals
Route: Oral gavage
Dosing Volume: 10 mL/kg Main study and Metabolism animals

Dose Vehicle: Water
Dosing Frequency: Daily
Day 0-Day 6 Main study animals
Day 0-Day 7 Metabolism animals
Blood Sample Frequency: Day 7 Metabolism animals; predose, 0.25, 0.5, 1, 2, 4, 8, 12, 24,
48, 72, 96, 120, 144, and 168 hours post dose via tail vein.

PARAMETERS

Clinical signs, body weight, clinpath (SE=D7), necropsy, organ weight, P450s, β -oxidation, AUC

METHODS

LC/MS Sample Analyses

A. Plasma Samples

The plasma samples were received and stored frozen prior to laboratory use. The samples were prepared for analysis by pipeting 150 μL acetonitrile into a 1.7 mL microcentrifuge tube, and pipeting 50.0 μL of plasma sample. The sample tubes were then vortexed for 1 minute and centrifuged at 14,000 RCF for 30 minutes. After centrifugation, 100 μL of sample supernatant was placed into a HPLC vial and 400 μL of HPLC grade water was added and mixed. As necessary, additional sample dilutions were performed using the 15% acetonitrile in HPLC grade water solvent to ensure that the sample responses were within the calibration curve.

B. Liver and Fat Samples

The liver and fat samples were received and stored frozen prior to laboratory use. The liver tissue samples were extracted in Acetonitrile with 4% perchloric acid while the fat samples were extracted in isopropyl alcohol. The calibration standards were prepared in the appropriate matched solvents.

1. Fat and Liver Extract Preparation.

The fat and liver samples were preprocessed by chopping the tissue samples into small pieces and weighing (0.5 grams) into disposable 15-mL polypropylene centrifuge tubes. Five 5/32" ball bearings were added to each tube, and a pipet was used to add 5000 μL of the appropriate extraction solvent. The tubes were sealed with parafilm, and inserted into a SPEX Certiprep Genogrinder and homogenized for 4 minutes at 1400 strokes/minute. After homogenization, the tubes were centrifuge at 4125 rpm for 20 min at room temperature. The extract supernatant was transferred into glass vials and frozen prior to further sample preparation.

2. Fat and Liver Extract Analysis.

Fat and Liver Extract Analysis. Approximately 100 mg of Envi-Carb graphitized carbon sorbent was placed into a 1.7-mL microcentrifuge tube. A pipet was used to add 50.0 μL of glacial acetic acid directly to the sorbent. Next, a pipet was used to add 1000 μL of sample extract into the centrifuge tube. The tubes were capped, vortexed briefly, and then centrifuged at 10,000 RCF for 10 minutes at room temperature. After centrifugation, a pipet was used to add 525 μL of the 1.7-mL microcentrifuge tube supernatant into a new 1.7 mL microcentrifuge tube and 475 μL of HPLC grade water and mixed. The samples were centrifuged at 10,000 RCF for 5 minutes at room temperature, and supernatant transferred into HPLC vials for analysis. As necessary, additional sample dilutions were performed using the matched solvent to ensure that the sample responses were within the calibration curve.

The prepared samples were analyzed by LC/MS using the following parameters:

HPLC Instrument: Agilent Model 1200
MS Instrument: Applied Biosystems API 4000

LC Parameters:

Column: Zorbax RX-C8, 150 x 2.1 mm, 5 µm particle size
Mobile Phase: A: 0.15% acetic acid and 0.15% triethyl amine in HPLC grade water
B: 0.15% acetic acid and 0.15% triethyl amine in acetonitrile

Column Temperature: 35°C
Injection Volume: 10 µL

MS Parameters:

Ion Source: Turbo Spray, Negative Ion
Temperature (TEM): 450
Dwell: 300 msec
Curtain Gas Flow (CUR): 50.0
GS1: 11
GS2: 70
IonSpray (IS) Voltage: -4500
CAD: 10.0
EP: -10.0
Quadrupole Resolution: Quad. 1: Unit
Quad. 3: Unit

MRM Settings Q1 Mass Q3 Mass DP CE CXP
 329.00 285.00 -20 -10 -5

HPLC Gradient Total Time Flow Rate
 (min) (mL/min) A(%) B(%)
 0.00 250 60.0 40.0
 5.00 250 60.0 40.0
 5.01 350 10.0 90.0
 9.00 350 10.0 90.0
 9.01 350 60.0 40.0
 19.00 350 60.0 40.0
 19.01 250 60.0 40.0
 20.00 250 60.0 40.0

RESULTS

The individual plasma sample results are provided in Appendix A

The individual liver sample results are provided in Appendix B

The individual fat sample results are provided in Appendix C

The summary and individual clinical pathology results are provided in Appendix D

The summary and individual pathology results are provided in Appendix E

The individual mechanistic evaluation results are provided in Appendix F

Dose (mg/kg/day)	30	300	1000	30	300	1000
	Male			Female		
Deaths:	0/8	0/5	0/5	0/8	0/5	0/5
Comment:	No deaths.					
Clinical Signs:	0/8	0/5	0/5	0/8	0/5	0/5
Comment:	No treatment related clinical observations in either sex at any dose level.					

Body Weights:	Animal body weights on test day 7 reported as percent of control: Male low dose (30 mg/kg): 99.9% of control \pm 4.7% Male mid dose (300 mg/kg): 99.1% of control \pm 4.2% Male high dose (1000 mg/kg): 92.4% of control \pm 2.0% Female low dose (30 mg/kg): 103.7% of control \pm 8.7% Female mid dose (300 mg/kg): 103.6% of control \pm 8.2% Female high dose (1000 mg/kg): 103.9% of control \pm 8.4% Effect on body weight was significant at the high dose level in male rats (p<0.05)
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Graphs:



Vales shown are mean \pm standard deviation.

In the summary tables below, statistically significant values ($p \leq 0.05$) are given in bold.

Dose (mg/kg/day)	0	30	300	1000	0	30	300	1000
Hematology	Male				Female			
RBC Day 7	7.54 0.53(5)	7.16 0.43(5) 95%	6.64 0.50(5) 88%	6.24 0.95(5) 83%	7.83 0.30(5)	7.93 0.29(5) 101%	7.50 0.29(5) 96%	6.43 0.75(5) 82%
HGB Day 7	14.8 0.4(5)	14.4 0.4(5) 97%	13.2 0.6(5) 89%	12.2 1.6(5) 82%	15.3 0.4(5)	15.8 0.4(5) 103%	14.8 0.4(5) 97%	12.9 1.2(5) 84%
HCT Day 7	46.5 1.5(5)	45.3 1.3(5) 97%	41.6 2.0(5) 89%	38.9 4.7(5) 84%	46.6 1.3(5)	47.8 1.2(5) 103%	45.0 1.7(5) 97%	39.7 2.8(5) 85%
RDW Day 7	12.4 0.4(5)	13.0 0.4(5) 105%	13.0 0.4(5) 105%	14.0 1.6(5) 113%	11.1 0.3(5)	11.0 0.2(5) 99%	11.5 0.5(5) 104%	12.8 1.9(5) 115%
ARET Day 7	305.8 26.8(5)	276.1 47.0(5) 90%	305.5 23.8(5) 100%	297.5 137.3(5) 97%	183.4 28.5(5)	189.9 33.2(5) 104%	244.5 108.5(5) 133%	473.4 318.3(5) 258%
ANEU Day 7	1.78 0.54(5)	1.63 0.53(5) 100%	1.62 0.69(5) 93%	2.75 1.79(5) 154%	0.89 0.25(5)	1.41 0.47(5) 168%	0.78 0.27(5) 93%	1.49 0.28(5) 215%
Comment:	Statistically significant decreases in red cell mass parameters (red blood cell, hemoglobin and hematocrit) were observed in male rats at 300 and 1000 mg/kg/day and in females at 1000 mg/kg/day. Statistically significant increases in red cell distribution width, reticulocytes and neutrophils were also present in 1000 mg/kg/day females.							

Dose (mg/kg/day)	0	30	300	1000	0	30	300	1000
Serum Chemistry	Male				Female			
AST Day 7	79 14(5)	81 16(5) 103%	83 12(5) 105%	108 5(5) 137%	82 18(5)	86 14(5) 105%	82 9(5) 100%	95 16(5) 116%
ALT Day 7	26 3(5)	29 6(5) 112%	32 6(5) 123%	48 6(5) 185%	20 2(5)	22 3(5) 110%	26 3(5) 130%	29 4(5) 145%
SDH Day 7	17.1 5.0(5)	16.9 2.9(5) 99%	11.8 5.4(5) 69%	5.2 3.6(5) 30%	13.7 7.2(5)	9.1 6.4(5) 66%	14.5 5.7(5) 106%	9.7 3.5(5) 71%
BILI Day 7	0.13 0.01(5)	0.11 0.02(5) 85%	0.13 0.01(5) 100%	0.13 0.02(5) 115%	0.13 0.02(5)	0.12 0.01(5) 92%	0.12 0.01(5) 92%	0.10 0.01(5) 77%
BUN Day 7	11 1(5)	11 1(5) 100%	14 1(5) 127%	15 2(5) 136%	15 3(5)	12 1(5) 80%	14 2(5) 93%	11 2(5) 73%
CREA Day 7	0.32 0.01(5)	0.29 0.03(5) 91%	0.29 0.02(5) 91%	0.27 0.03(5) 84%	0.37 0.02(5)	0.35 0.02(5) 95%	0.35 0.03(5) 95%	0.30 0.03(5) 81%
CHOL Day 7	69 9(5)	36 9(5) 52%	38 9(5) 55%	37 9(5) 54%	73 11(5)	59 6(5) 81%	55 13(5) 75%	52 10(5) 71%
TRIG Day 7	79 31(5)	36 8(5) 46%	37 9(5) 47%	34 9(5) 43%	57 32(5)	35 6(5) 61%	31 6(5) 54%	33 5(5) 58%
GLUC Day 7	78 6(5)	90 12(5) 115%	99 5(5) 127%	98 14(5) 126%	93 4(5)	91 7(5) 98%	86 9(5) 92%	93 17(5) 100%
TP Day 7	6.1 0.2(5)	5.9 0.4(5) 97%	5.5 0.3(5) 90%	4.8 0.3(5) 79%	6.6 0.5(5)	6.6 0.3(5) 100%	6.1 0.3(5) 92%	5.6 0.3(5) 85%
Albumin Day 7	3.5 0.1(5)	3.8 0.3(5) 109%	3.7 0.2(5) 106%	3.3 0.2(5) 94%	4.0 0.3(5)	4.0 0.2(5) 100%	3.8 0.2(5) 95%	3.6 0.2(5) 90%
Globulin Day 7	2.5 0.1(5)	2.1 0.1(5) 84%	1.8 0.2(5) 72%	1.6 0.2(5) 64%	2.6 0.2(5)	2.6 0.2(5) 100%	2.3 0.2(5) 88%	2.0 0.2(5) 77%
CALC Day 7	10.6 0.2(5)	10.6 0.3(5) 100%	10.3 0.2(5) 97%	9.8 0.2(5) 92%	10.5 0.6(5)	10.4 0.3(5) 99%	10.3 0.4(5) 98%	10.0 0.2(5) 95%
Sodium Day 7	146.5 1.1(5)	145.7 1.3(5) 99%	145.8 0.9(5) 100%	144.0 1.1(5) 98%	144.8 1.2(5)	144.6 0.6(5) 100%	145.0 1.7(5) 100%	144.3 0.7(5) 100%
Comment:	Decreases in serum lipids (triglycerides and/or cholesterol) and globulins were present in all dosed male groups and in females at 300 and/or 1000 mg/kg/day. Other changes in clinical chemistry parameters occurred at 300 and/or 1000 mg/kg/day and included increased ALT, AST, BUN, and Glucose; and decreased SDH, creatinine, and calcium.							

Gross Path	Male	Female
Observations:	No test-substance related gross findings.	No test-substance related gross findings.

Dose (mg/kg/day)	0	30	300	1000	0	30	300	1000
Organ Weights	Male				Female			
Final Body Weight (g)	287.5 4.1(5)	287.4 15.8(5) 100%	284.9 8.9(5) 99%	265.8 7.1(5) 92%	185.9 6.9(5)	192.3 11.0(5) 103%	192.2 9.0(5) 103%	192.7 10.0(5) 104%
Absolute Heart (g)	1.212 0.086(5)	1.233 0.086(5) 102%	1.134 0.068(5) 94%	0.988 0.096(5) 82%	0.842 0.070(5)	1.205 0.769(5) 143%	0.827 0.059(5) 98%	0.799 0.030(5) 95%
Heart/Brain %	61.430 4.332(5)	61.838 4.676(5) 101%	58.521 4.094(5) 95%	51.438 3.544(5) 84%	44.872 4.355(5)	66.012 44.521(5) 147%	44.859 3.288(5) 100%	43.289 1.949(5) 96%
Heart/Body %	0.421 0.027(5)	0.429 0.017(5) 102%	0.398 0.028(5) 95%	0.372 0.035(5) 88%	0.454 0.039(5)	0.646 0.466(5) 142%	0.431 0.032(5) 95%	0.415 0.008(5) 91%
Absolute Liver (g)	10.991 1.444(5)	15.148 3.132(5) 138%	17.864 0.777(5) 163%	15.457 1.881(5) 141%	6.536 0.367(5)	6.679 0.602(5) 102%	6.497 0.682(5) 99%	8.127 0.713(5) 124%
Liver/Brain %	557.139 73.755(5)	761.435 170.426(5) 137%	921.173 42.150(5) 165%	805.185 85.825(5) 145%	348.073 23.563 (5)	360.927 26.217(5) 104%	351.980 32.524(5) 101%	440.752 44.231(5) 127%
Liver/Body %	3.818 0.463	5.242 0.841(5) 137%	6.273 0.315(5) 164%	5.816 0.709(5) 152%	3.517 0.170(5)	3.469 0.152(5) 99%	3.378 0.260(5) 96%	4.229 0.450(5) 120%
Brain/Body %	0.686 0.010(5)	0.696 0.049(5) 101%	0.681 0.013(5) 99%	0.722 0.018(5) 105%	1.012 0.037(5)	0.963 0.041(5) 95%	0.961 0.049(5) 95%	0.960 0.061(5) 95%
Absolute Kidneys (g)	2.534 0.107(5)	2.915 0.438(5) 115%	2.690 0.127(5) 106%	2.552 0.178(5) 101%	1.611 0.064(5)	1.792 0.186(5) 111%	1.710 0.100(5) 106%	1.854 0.117(5) 115%
Kidneys/Brain %	128.450 5.735(5)	146.026 21.816(5) 114%	138.766 8.330(5) 108%	132.980 5.494(5) 104%	85.739 3.810(5)	96.795 7.889(5) 113%	92.755 5.781(5) 108%	100.552 7.920(5) 117%
Kidney/Body %	0.881 0.031(5)	1.012 0.121(5) 115%	0.946 0.071(5) 107%	0.960 0.060(5) 109%	0.868 0.060(5)	0.932 0.079(5) 107%	0.890 0.043(5) 103%	0.963 0.064(5) 111%
Comment:	Increased liver weight parameters were present in males at all dose levels and in females in the 1000 mg/kg/day group. These liver weight changes were correlative to microscopic hepatocellular hypertrophy in the liver. Other organ weight changes included decreases in heart weight parameters (1000 mg/kg/day males) and increases in some kidney weight parameters (1000 mg/kg/day females). There were no correlative microscopic changes in these organs.							

Dose (mg/kg/day)	0	30	300	1000	0	30	300	1000
Histopath	Male				Female			
Comment:	Test substance-related microscopic changes were limited to hepatocellular hypertrophy in the liver. Minimal to mild hypertrophy was present in male rats at all doses and in females administered 1000 mg/kg/day. Microscopic and organ weight changes in the liver were associated with increases in B-oxidation and/or increases in total P450 enzyme activity.							

Dose (mg/kg/day)	30	
Plasma PK	Male	Female
Fat:plasma ratio	ND	ND
Liver:plasma ratio	1.4	3.8*
Comment:	Fat: plasma ratio not determined; all fat values below LOQ. * n=2	
Clearance time (h):	46	4
Comment:	<p>Based on the experimental design, the pharmacokinetic graphs resulting from this class of chemicals makes traditional methods of half-life calculation inappropriate. In order to provide a basis for comparing these chemicals to each other, the clearance time of the analyte will be calculated instead. In traditional pharmacokinetics an analyte is considered to be completely cleared after 98.4% of the analyte is cleared from the plasma.</p> <p>This clearance time calculation is impacted by one male having a slightly higher AUC than the other two individuals. Given the low number of animals on this study (n = 3), the fact that a plasma sample taken on Day 6 at 2 hrs post dose and another taken on Day 7 at 2 hrs were very similar in concentration, it is likely that the calculated clearance time of 46 hrs is longer than the true value.</p>	

Dose (mg/kg/day)	30	
Plasma PK	Male	Female
Graph:	<p>The top graph shows plasma concentration (ng/ml) on a logarithmic scale from 10 to 100,000 against time (hr) from 0 to 168. Males (squares) show a concentration of approximately 100,000 ng/ml at 0 hours, decreasing to about 200 ng/ml by 168 hours. Females (circles) show a concentration of approximately 100,000 ng/ml at 0 hours, decreasing to about 20 ng/ml by 168 hours. Error bars are included for each data point.</p> <p>The bottom graph shows plasma concentration (ng/ml) on a logarithmic scale from 1 to 100,000 for males and females at 2 hours post-dose on Day 6 (dotted bars) and Day 7 (hatched bars). For males, concentrations are approximately 60,000 ng/ml on Day 6 and 60,000 ng/ml on Day 7. For females, concentrations are approximately 20,000 ng/ml on Day 6 and 6,000 ng/ml on Day 7.</p>	
Comment:	Plasma concentration at 2 hrs post dose on two consecutive days of dosing. Plasma concentration on two consecutive days of dosing is similar, implying that there is no accumulation in the rat following repeated dosing. The LOQ is approximately 20 ng/mL.	

Dose (mg/kg/day)	30	300	1000
Total P450:	M – No stat. sign. effect F – No stat. sign. effect	M – 169% of control* F – No stat. sign. effect	M – 182% of control* F – 123% of control*
Comment:			
β-oxidation:	M – 695% of control* F – No stat. sign. effect	M – 986% of control* F – No stat. sign. effect	M – 1040% of control* F – 542% of control@
Comment:	* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test @ Statistically significant difference from control ($p \leq 0.05$) by Dunn's test stat. sign. = statistically significant		

Appendix A
Individual LC/MS Plasma Sample Results

H-28308 Plasma Concentration for the specified timepoint (ng/mL)

Rat Number	Predose	15 min	30 min	1 Hour	2 Hour	4 Hour	8 Hour	12 Hour	24 Hour	48 Hour	72 Hour	96 Hour	120 Hour	144 Hour	168 Hour	2 Hr post-dose
Rat #206	4920	41000	63600	62800	81600	31280	12540	5900	1582	686	316	300	210	138	166	60400
Rat #207	3600	36200	50800	65600	63600	42800	12000	8680	2060	512	1000	148	182	191	206	52600
Rat #208	6060	62600	73800	68000	58800	59200	21400	12200	6440	1594	960	746	520	412	366	67600
Rat #256	30.0	68800	61200	40400	25120	1150	380	288	224	29.2	21.2	44.6	<LOQ	<LOQ	23.0	4380
Rat #257	32.5	48200	72800	37040	19160	410	370	526	145	25.8	<LOQ	38.2	<LOQ	<LOQ	25.6	4700
Rat #258	80.0	97200	86200	39400	16280	1304	159	378	103	41.6	33.8	32.6	<LOQ	21.8	<LOQ	7500

H-28308 Plasma Concentration for the specified timepoint (ng/mL)

Rat Number	Predose	15 min	30 min	1 Hour	2 Hour	4 Hour	8 Hour	12 Hour	24 Hour	48 Hour	72 Hour	96 Hour	120 Hour	144 Hour	168 Hour	2 Hr post-dose
Rat #206	4920	41000	63600	62800	81600	31280	12540	5900	1582	686	316	300	210	138	166	60400
Rat #207	3600	36200	50800	65600	63600	42800	12000	8680	2060	512	1000	148	182	191	206	52600
Rat #208	6060	62600	73800	68000	58800	59200	21400	12200	6440	1594	960	746	520	412	366	67600
Rat #256	30	68800	61200	40400	25120	1150	380	288	224	29.2	21.2	44.6	20	20	23	4380
Rat #257	32.5	48200	72800	37040	19160	410	370	526	145	25.8	20	38.2	20	20	25.6	4700
Rat #258	80	97200	86200	39400	16280	1304	159	378	103	41.6	33.8	32.6	20	21.8	20	7500

Appendix B
Individual LC/MS Liver Sample Results

		H-28308 Concentration (ng/g)
Males	30 mg/kg Rat #206	284
	30 mg/kg Rat #207	285
	30 mg/kg Rat #208	417
Females	30 mg/kg Rat #256	109
	30 mg/kg Rat #257	75.6
	30 mg/kg Rat #258	225

Appendix C
Individual LC/MS Fat Sample Results

		H-28308 Concentration (ng/g)
Males	30 mg/kg Rat #206	<LOQ
	30 mg/kg Rat #207	<LOQ
	30 mg/kg Rat #208	<LOQ
Females	30 mg/kg Rat #256	<LOQ
	30 mg/kg Rat #257	<LOQ
	30 mg/kg Rat #258	<LOQ

Appendix D
Summary and Individual Animal Clinical Pathology Data

EXPLANATORY NOTES

ABBREVIATIONS:

General:

Adeq - adequate
Decr - decreased
Mod - moderate
OK - sample condition OK for testing
UTD - unable to determine
- - not observed, no data
. - not taken, not performed, not observed, or results not valid

Individual Hematology Values:

WB - whole blood condition
RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular (cell) volume
MCH - mean corpuscular (cell) hemoglobin
MCHC - mean corpuscular (cell) hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell
NRBC - nucleated red blood cell count
ARL - absolute reactive lymphocyte
AATL - absolute atypical lymphocyte
AIM - absolute immature monocyte
NC - not calculated or not calculable

Individual Red Blood Cell / White Blood Cell / Platelet Morphology Values:

ANIS - anisocytosis
MIC - microcytes
MAC - macrocytes
POLY - polychromasia
HYPO - hypochromasia
ECHI - echinocytes
ACAN - acanthocytes
TARG - target cells
RX - rouleaux
HJB - Howell-Jolly body
SM - smudge white blood cells
TOX - toxic granulation
DB - Döhle bodies
VC - vacuolated cytoplasm
BC - basophilic cytoplasm
PCE - platelet clumps / estimate
GP - giant platelets
BP - bizarre platelets

Individual Clinical Chemistry Values:

HEM - hemolysis
LIP - lipemia
ICT - icterus
AST - aspartate aminotransferase
ALT - alanine aminotransferase
SDH - sorbitol dehydrogenase
ALKP - alkaline phosphatase
BILI - total bilirubin
BUN - urea nitrogen
CREA - creatinine
CHOL - cholesterol

TRIG - triglycerides
GLUC - glucose
TP - total protein
ALB - albumin
GLOB - globulin
CALC - calcium
IPHS - inorganic phosphorous
NA - sodium
K - potassium
CL - chloride

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:

the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

Summary of Hematology Values for Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
RBC ($\times 10^6/\mu\text{L}$)				
DAY 7	7.54 0.53(5)	7.16 0.43(5)	6.64 0.50(5)	6.24* 0.95(5)
HGB (g/dL)				
DAY 7	14.8 0.4(5)	14.4 0.4(5)	13.2* 0.6(5)	12.2* 1.6(5)
HCT (%)				
DAY 7	46.5 1.5(5)	45.3 1.3(5)	41.6* 2.0(5)	38.9* 4.7(5)
MCV (fL)				
DAY 7	61.9 2.8(5)	63.3 3.4(5)	62.8 2.3(5)	62.6 4.2(5)
MCH (pg)				
DAY 7	19.7 0.9(5)	20.1 0.9(5)	19.9 0.8(5)	19.6 1.4(5)
MCHC (g/dL)				
DAY 7	31.9 0.4(5)	31.7 0.3(5)	31.8 0.4(5)	31.4 0.3(5)
RDW (%)				
DAY 7	12.4 0.4(5)	13.0 0.4(5)	13.0 0.4(5)	14.0 1.6(5)
ARET ($\times 10^3/\mu\text{L}$)				
DAY 7	305.8 26.8(5)	276.1 47.0(5)	305.5 23.8(5)	297.5 137.3(5)
PLT ($\times 10^3/\mu\text{L}$)				
DAY 7	1312 NC(1)	1473 117(5)	1651 191(3)	1418 247(5)
WBC ($\times 10^3/\mu\text{L}$)				
DAY 7	16.29 1.45(5)	13.31* 0.92(5)	14.16 2.23(5)	18.76 1.43(5)
ANEU ($\times 10^3/\mu\text{L}$)				
DAY 7	1.78 0.54(5)	1.63 0.53(5)	1.62 0.69(5)	2.75 1.79(5)
ALYM ($\times 10^3/\mu\text{L}$)				
DAY 7	13.83 1.54(5)	11.15* 0.99(5)	11.94 1.50(5)	15.15 1.39(5)
AMON ($\times 10^3/\mu\text{L}$)				
DAY 7	0.33 0.03(5)	0.20 0.05(5)	0.30 0.18(5)	0.35 0.11(5)
AEOS ($\times 10^3/\mu\text{L}$)				
DAY 7	0.13 0.05(5)	0.06 0.03(5)	0.12 0.05(5)	0.17 0.12(5)
ABAS ($\times 10^3/\mu\text{L}$)				
DAY 7	0.12 0.03(5)	0.07 0.04(5)	0.07 0.05(5)	0.18 0.12(5)
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 7	0.11 0.02(5)	0.06 0.04(5)	0.08 0.06(5)	0.16 0.07(5)

NRBC (/100 WBC)				
DAY 7	-	-	1~	-
			NC(1)	
ARL ($\times 10^3/\mu\text{L}$)				
DAY 7	-	0.28~	-	-
		NC(1)		
AATL ($\times 10^3/\mu\text{L}$)				
DAY 7	-	-	0.11~	-
			NC(1)	
AIM ($\times 10^3/\mu\text{L}$)				
DAY 7	-	0.43~	-	-
		NC(1)		

Data arranged as: Mean
 Standard deviation (Number of values included in calculation)

- * Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
- @ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
- ~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Summary of Hematology Values for Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
RBC ($\times 10^6/\mu\text{L}$)				
DAY 7	7.83 0.30(5)	7.93 0.29(5)	7.50 0.29(5)	6.43* 0.75(5)
HGB (g/dL)				
DAY 7	15.3 0.4(5)	15.8 0.4(5)	14.8 0.4(5)	12.9* 1.2(5)
HCT (%)				
DAY 7	46.6 1.3(5)	47.8 1.2(5)	45.0 1.7(5)	39.7* 2.8(5)
MCV (fL)				
DAY 7	59.5 1.8(5)	60.3 1.5(5)	60.1 1.3(5)	61.9 3.3(5)
MCH (pg)				
DAY 7	19.6 0.6(5)	19.9 0.6(5)	19.7 0.4(5)	20.2 0.6(5)
MCHC (g/dL)				
DAY 7	32.9 0.2(5)	33.1 0.2(5)	32.8 0.3(5)	32.6 0.9(5)
RDW (%)				
DAY 7	11.1 0.3(5)	11.0 0.2(5)	11.5 0.5(5)	12.8* 1.9(5)
ARET ($\times 10^3/\mu\text{L}$)				
DAY 7	183.4 28.5(5)	189.9 33.2(5)	244.5 108.5(5)	473.4* 318.3(5)
PLT ($\times 10^3/\mu\text{L}$)				
DAY 7	1334 226(3)	1477 NC(1)	1334 NC(1)	1438 193(5)
WBC ($\times 10^3/\mu\text{L}$)				
DAY 7	10.13 0.59(5)	12.14 2.30(5)	11.80 2.89(5)	12.70 3.30(5)
ANEU ($\times 10^3/\mu\text{L}$)				
DAY 7	0.89 0.25(5)	1.41 0.47(5)	0.78 0.27(5)	1.49* 0.28(5)
ALYM ($\times 10^3/\mu\text{L}$)				
DAY 7	8.73 0.73(5)	10.21 2.27(5)	10.56 2.72(5)	10.63 3.13(5)
AMON ($\times 10^3/\mu\text{L}$)				
DAY 7	0.18 0.06(5)	0.21 0.10(5)	0.17 0.05(5)	0.17 0.05(5)
AEOS ($\times 10^3/\mu\text{L}$)				
DAY 7	0.12 0.03(5)	0.11 0.02(5)	0.12 0.03(5)	0.17 0.07(5)
ABAS ($\times 10^3/\mu\text{L}$)				
DAY 7	0.08 0.05(5)	0.10 0.07(5)	0.10 0.03(5)	0.06 0.08(5)
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 7	0.09 0.05(5)	0.09 0.06(5)	0.07 0.02(5)	0.09 0.08(5)

NRBC (/100 WBC)	-	-	-	1~
DAY 7				NC(1)
AATL ($\times 10^3/\mu\text{L}$)	0.29~	-	-	0.44~
DAY 7	NC(1)			NC(1)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- * Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
- @ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
- ~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Summary of Clinical Chemistry Values for Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
AST (U/L)				
DAY 7	79 14(5)	81 16(5)	83 12(5)	108* 5(5)
ALT (U/L)				
DAY 7	26 3(5)	29 6(5)	32 6(5)	48* 6(5)
SDH (U/L)				
DAY 7	17.1 5.0(5)	16.9 2.9(5)	11.8 5.4(5)	5.2* 3.6(5)
ALKP (U/L)				
DAY 7	243 69(5)	258 85(5)	301 26(5)	325 40(5)
BILI (mg/dL)				
DAY 7	0.13 0.01(5)	0.11 0.02(5)	0.13 0.01(5)	0.15 0.02(5)
BUN (mg/dL)				
DAY 7	11 1(5)	11 1(5)	14* 1(5)	15* 2(5)
CREA (mg/dL)				
DAY 7	0.32 0.01(5)	0.29 0.03(5)	0.29 0.02(5)	0.27* 0.03(5)
CHOL (mg/dL)				
DAY 7	69 9(5)	36* 9(5)	38* 9(5)	37* 9(5)
TRIG (mg/dL)				
DAY 7	79 31(5)	36@ 8(5)	37 9(5)	34@ 9(5)
GLUC (mg/dL)				
DAY 7	78 6(5)	90 12(5)	99* 5(5)	98* 14(5)
TP (g/dL)				
DAY 7	6.1 0.2(5)	5.9 0.4(5)	5.5* 0.3(5)	4.8* 0.3(5)
ALB (g/dL)				
DAY 7	3.5 0.1(5)	3.8 0.3(5)	3.7 0.2(5)	3.3 0.2(5)
GLOB (g/dL)				
DAY 7	2.5 0.1(5)	2.1* 0.1(5)	1.8* 0.2(5)	1.6* 0.2(5)
CALC (mg/dL)				
DAY 7	10.6 0.2(5)	10.6 0.3(5)	10.3* 0.2(5)	9.8* 0.2(5)
IPHS (mg/dL)				
DAY 7	9.6 0.3(5)	9.5 0.3(5)	9.3 0.5(5)	8.9 0.7(5)
NA (mmol/L)				
DAY 7	146.5 1.1(5)	145.7 1.3(5)	145.8 0.9(5)	144.0* 1.1(5)

K (mmol/L)				
DAY 7	6.06	6.29	6.39	6.18
	0.30(5)	0.34(5)	0.15(5)	0.44(5)
CL (mmol/L)				
DAY 7	98.8	97.6	100.0	100.3
	2.0(5)	1.5(5)	1.1(5)	1.4(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- * Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
- @ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
- ~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Summary of Clinical Chemistry Values for Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
AST (U/L)				
DAY 7	82 18(5)	86 14(5)	82 9(5)	95 16(5)
ALT (U/L)				
DAY 7	20 2(5)	22 3(5)	26* 3(5)	29* 4(5)
SDH (U/L)				
DAY 7	13.7 7.2(5)	9.1 6.4(5)	14.5 5.7(5)	9.7 3.5(5)
ALKP (U/L)				
DAY 7	113 22(5)	121 32(5)	129 30(5)	108 20(5)
BILI (mg/dL)				
DAY 7	0.13 0.02(5)	0.12 0.01(5)	0.12 0.01(5)	0.10* 0.01(5)
BUN (mg/dL)				
DAY 7	15 3(5)	12 1(5)	14 2(5)	11 2(5)
CREA (mg/dL)				
DAY 7	0.37 0.02(5)	0.35 0.02(5)	0.35 0.03(5)	0.30@ 0.03(5)
CHOL (mg/dL)				
DAY 7	73 11(5)	59 6(5)	55* 13(5)	52* 10(5)
TRIG (mg/dL)				
DAY 7	57 32(5)	35 6(5)	31 6(5)	33 5(5)
GLUC (mg/dL)				
DAY 7	93 4(5)	91 7(5)	86 9(5)	93 17(5)
TP (g/dL)				
DAY 7	6.6 0.5(5)	6.6 0.3(5)	6.1 0.3(5)	5.6* 0.3(5)
ALB (g/dL)				
DAY 7	4.0 0.3(5)	4.0 0.2(5)	3.8 0.2(5)	3.6 0.2(5)
GLOB (g/dL)				
DAY 7	2.6 0.2(5)	2.6 0.2(5)	2.3 0.2(5)	2.0* 0.2(5)
CALC (mg/dL)				
DAY 7	10.5 0.6(5)	10.4 0.3(5)	10.3 0.4(5)	10.0 0.2(5)
IPHS (mg/dL)				
DAY 7	6.8 0.3(5)	7.5 0.7(5)	7.4 0.7(5)	7.5 0.7(5)
NA (mmol/L)				
DAY 7	144.8 1.2(5)	144.6 0.6(5)	145.0 1.7(5)	144.3 0.7(5)

K (mmol/L)				
DAY 7	5.49	5.54	5.60	5.55
	0.19(5)	0.51(5)	0.23(5)	0.14(5)
CL (mmol/L)				
DAY 7	100.6	101.3	101.6	101.4
	1.4(5)	1.8(5)	2.7(5)	1.5(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- * Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
- @ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
- ~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	WB	RBC x10 ⁶ /uL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL
1m	101	7	OK	7.53	15.0	46.6	62.0	19.9	32.1
	102	7	OK	6.81	14.3	44.3	65.1	20.9	32.2
	103	7	OK	7.65	15.0	48.0	62.7	19.6	31.3
	104	7	OK	7.40	14.6	46.0	62.2	19.7	31.8
	105	7	OK	8.29	15.2	47.6	57.5	18.4	32.0
2m	201	7	OK	7.32	14.2	44.6	60.9	19.4	31.9
	202	7	OK	6.92	14.2	44.3	64.0	20.4	31.9
	203	7	OK	6.69	14.4	46.0	68.8	21.5	31.2
	204	7	OK	7.06	14.0	44.2	62.5	19.8	31.7
	205	7	OK	7.81	15.1	47.3	60.5	19.4	32.0
3m	301	7	OK	6.21	12.8	39.7	63.9	20.7	32.4
	302	7	OK	6.91	13.6	43.3	62.7	19.6	31.3
	303	7	OK	6.58	12.9	40.4	61.4	19.5	31.8
	304	7	OK	6.15	12.8	40.6	66.0	20.8	31.5
	305	7	OK	7.36	14.1	44.2	60.1	19.1	31.8
4m	401	7	OK	5.43	10.8	34.8	64.1	19.9	31.0
	402	7	OK	6.53	11.6	37.0	56.7	17.7	31.2
	403	7	OK	6.83	13.6	42.6	62.3	19.8	31.8
	404	7	OK	7.33	14.2	45.1	61.6	19.3	31.4
	405	7	OK	5.09	11.0	34.9	68.4	21.5	31.4
1f	151	7	OK	7.63	15.0	45.7	59.8	19.7	32.9
	152	7	OK	7.77	14.9	45.3	58.3	19.1	32.8
	153	7	OK	7.81	15.7	48.2	61.7	20.1	32.6
	154	7	OK	8.34	15.8	47.7	57.2	18.9	33.1
	155	7	OK	7.62	15.3	46.2	60.7	20.1	33.2
2f	251	7	OK	7.89	16.1	48.6	61.6	20.4	33.2
	252	7	OK	8.05	15.9	48.2	59.9	19.7	32.9
	253	7	OK	8.15	16.2	48.9	60.1	19.9	33.2
	254	7	OK	8.13	15.6	47.3	58.2	19.1	32.9
	255	7	OK	7.44	15.3	46.0	61.8	20.6	33.3
3f	351	7	OK	7.34	14.8	45.5	62.0	20.1	32.5
	352	7	OK	7.37	14.4	43.6	59.2	19.5	32.9
	353	7	OK	7.48	15.0	45.6	60.9	20.0	32.9
	354	7	OK	8.01	15.4	47.4	59.2	19.2	32.5
	355	7	OK	7.29	14.3	43.1	59.1	19.7	33.3
4f	451	7	OK	5.54	11.5	35.9	64.8	20.8	32.0
	452	7	OK	6.69	13.4	41.6	62.1	20.1	32.3
	453	7	OK	5.74	11.9	37.5	65.3	20.7	31.7
	454	7	OK	7.10	13.8	40.8	57.4	19.4	33.9
	455	7	OK	7.09	14.1	42.5	60.0	19.8	33.1

Individual Animal Clinical Pathology Data

Group	Animal Sex Number	Day Number	RDW %	ARET x10 ³ /uL	PLT x10 ³ /uL	WBC x10 ³ /uL	ANEU x10 ³ /uL	ALYM x10 ³ /uL	AMON x10 ³ /uL
1m	101	7	12.2	348.3	.	14.93	1.52	12.80	0.30
	102	7	12.6	308.9	.	15.14	2.55	11.86	0.33
	103	7	11.9	283.7	.	15.75	1.30	13.79	0.29
	104	7	12.9	281.8	1312	18.17	2.15	15.40	0.36
	105	7	12.4	306.1	.	17.46	1.38	15.28	0.36
2m	201	7	13.4	280.8	1437	14.20	1.00	12.35	0.14
	202	7	12.8	271.3	1579	14.05	1.80	11.76	0.24
	203	7	13.6	312.4	1359	12.51	2.23	9.83	0.16
	204	7	12.8	316.3	1613	13.62	1.94	11.24	0.26
	205	7	12.6	199.6	1375	12.17	1.16	10.58	0.19
3m	301	7	12.8	341.5	.	14.71	1.27	12.93	0.29
	302	7	13.1	293.0	.	14.80	1.50	12.61	0.39
	303	7	13.6	317.0	1846	13.45	1.42	11.36	0.33
	304	7	13.0	293.6	1465	10.88	1.09	9.57	0.00
	305	7	12.7	282.2	1643	16.98	2.83	13.23	0.49
4m	401	7	14.8	339.0	1378	18.19	4.41	13.05	0.53
	402	7	16.4	223.5	1153	18.34	1.57	15.86	0.32
	403	7	12.7	214.8	1746	17.31	1.62	14.71	0.26
	404	7	12.6	189.6	1228	18.86	1.19	16.77	0.37
	405	7	13.3	520.4	1585	21.12	4.98	15.36	0.25
1f	151	7	11.5	197.9	.	9.67	1.02	8.21	0.14
	152	7	10.8	201.4	1474	9.99	0.76	8.64	0.22
	153	7	11.0	207.0	1073	10.08	0.66	8.92	0.26
	154	7	11.2	138.2	1454	11.13	0.73	9.86	0.17
	155	7	10.8	172.6	.	9.76	1.27	8.00	0.10
2f	251	7	10.9	199.4	1477	14.30	2.03	11.35	0.38
	252	7	11.2	218.6	.	13.25	1.25	11.52	0.22
	253	7	11.0	138.9	.	13.17	0.77	11.95	0.17
	254	7	11.2	176.2	.	11.53	1.36	9.82	0.14
	255	7	10.9	216.4	.	8.43	1.64	6.41	0.13
3f	351	7	12.1	355.1	.	12.78	0.88	11.43	0.14
	352	7	11.9	367.3	.	11.36	1.15	9.76	0.25
	353	7	11.1	169.7	.	8.29	0.51	7.40	0.13
	354	7	11.0	136.6	.	16.06	0.86	14.69	0.17
	355	7	11.3	193.8	1334	10.49	0.51	9.51	0.18
4f	451	7	14.4	683.2	1383	11.41	1.16	9.95	0.11
	452	7	11.8	295.0	1240	17.18	1.67	14.59	0.22
	453	7	15.2	929.4	1621	14.70	1.32	12.64	0.15
	454	7	11.0	193.6	1286	11.59	1.44	9.58	0.22
	455	7	11.5	265.7	1662	8.63	1.87	6.39	0.17

Individual Animal Clinical Pathology Data

Group	Animal	Day	AEOS	ABAS	ALUC	NRBC	ARL	AATL	AIM
Sex	Number	Number	x10 ³ /uL	x10 ³ /uL	x10 ³ /uL	/100 WBC	x10 ³ /uL	x10 ³ /uL	x10 ³ /uL
1m	101	7	0.14	0.08	0.08
	102	7	0.14	0.14	0.12
	103	7	0.15	0.10	0.12
	104	7	0.04	0.12	0.11
	105	7	0.18	0.15	0.11
2m	201	7	0.00	0.00	0.00	.	0.28	.	0.43
	202	7	0.08	0.11	0.06
	203	7	0.08	0.10	0.10
	204	7	0.06	0.06	0.06
	205	7	0.08	0.07	0.09
3m	301	7	0.05	0.06	0.10
	302	7	0.16	0.05	0.09
	303	7	0.12	0.14	0.07
	304	7	0.11	0.00	0.00	1	.	0.11	.
	305	7	0.16	0.11	0.16
4m	401	7	0.10	0.04	0.06
	402	7	0.38	0.09	0.12
	403	7	0.15	0.32	0.25
	404	7	0.14	0.21	0.19
	405	7	0.07	0.26	0.19
1f	151	7	0.14	0.07	0.09
	152	7	0.11	0.14	0.14
	153	7	0.09	0.07	0.09
	154	7	0.17	0.11	0.11
	155	7	0.10	0.00	0.00	.	.	0.29	.
2f	251	7	0.13	0.22	0.19
	252	7	0.10	0.10	0.06
	253	7	0.14	0.05	0.09
	254	7	0.08	0.08	0.06
	255	7	0.12	0.06	0.07
3f	351	7	0.11	0.14	0.08
	352	7	0.07	0.06	0.06
	353	7	0.13	0.08	0.04
	354	7	0.14	0.11	0.10
	355	7	0.14	0.09	0.07
4f	451	7	0.10	0.03	0.07
	452	7	0.27	0.20	0.22
	453	7	0.15	0.00	0.00	1	.	0.44	.
	454	7	0.21	0.04	0.09
	455	7	0.10	0.05	0.05

Individual Animal Clinical Pathology Data

Group	Animal Sex	Animal Number	Day Number	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX
1m		101	7	-	-	-	Trace	-	Mod	Few	-	-
		102	7	-	-	-	Trace	-	Trace	Trace	-	-
		103	7	-	-	-	Trace	-	Mod	Few	-	-
		104	7	-	-	-	Trace	-	Few	Trace	-	-
		105	7	Trace	Trace	-	Trace	-	Mod	Few	-	-
2m		201	7	-	-	-	Trace	-	Mod	Mod	-	-
		202	7	-	-	-	Trace	-	Few	Few	-	-
		203	7	-	-	-	Trace	-	Few	Trace	-	-
		204	7	-	-	-	Trace	-	Many	Mod	-	-
		205	7	-	-	-	-	-	Trace	Trace	-	-
3m		301	7	-	-	-	Trace	-	Mod	Few	-	-
		302	7	-	-	-	Trace	-	Mod	Few	-	-
		303	7	-	-	-	Trace	-	Many	Mod	-	-
		304	7	-	-	-	Trace	-	Many	Mod	-	-
		305	7	-	-	-	Trace	-	Many	Many	-	-
4m		401	7	-	-	-	Few	-	Few	Few	-	-
		402	7	Trace	Trace	-	Trace	Trace	Few	Trace	Trace	-
		403	7	-	-	-	Trace	-	Mod	Trace	-	-
		404	7	-	-	-	-	-	Mod	Few	-	-
		405	7	Trace	-	Trace	Few	-	Trace	-	-	-

Individual Animal Clinical Pathology Data

Group	Animal	Day	HJB	SM	TOX	DB	VC	BC	PCE	GP	BP
Sex	Number	Number									
1m	101	7	-	-	-	-	-	-	Adeq	Trace	-
	102	7	-	-	-	-	-	-	Adeq	Trace	-
	103	7	-	-	-	-	-	-	Adeq	-	-
	104	7	-	-	-	-	-	-	-	Trace	-
	105	7	-	-	-	-	-	-	Adeq	Trace	-
2m	201	7	Trace	-	-	-	-	-	-	Trace	-
	202	7	-	-	-	-	-	-	-	-	-
	203	7	-	-	-	-	-	-	-	-	-
	204	7	-	-	-	-	-	-	-	Trace	-
	205	7	-	-	-	-	-	-	-	-	-
3m	301	7	Trace	-	-	-	-	-	Adeq	Trace	-
	302	7	-	-	-	-	-	-	Adeq	Trace	-
	303	7	Trace	-	-	-	-	-	-	Trace	-
	304	7	-	-	-	-	-	-	-	Trace	-
	305	7	-	-	-	-	-	-	-	Trace	-
4m	401	7	-	-	-	-	-	-	-	Trace	-
	402	7	Trace	-	-	-	-	-	-	Trace	-
	403	7	-	-	-	-	-	-	-	-	-
	404	7	-	-	-	-	-	-	-	Trace	-
	405	7	Trace	-	-	-	-	-	-	Trace	-

Individual Animal Clinical Pathology Data

Group	Animal	Day	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX
Sex	Number	Number									
1f	151	7	Trace	Trace	-	-	-	Many	Few	-	-
	152	7	Trace	Trace	-	-	-	Mod	Few	-	-
	153	7	-	-	-	Trace	-	Few	Trace	-	-
	154	7	Trace	Trace	-	-	-	Many	Few	-	-
	155	7	-	-	-	-	-	Many	Mod	-	-
2f	251	7	-	-	-	-	-	Few	Trace	-	-
	252	7	-	-	-	Trace	-	Many	Few	-	-
	253	7	Trace	Trace	-	-	-	Many	Few	-	-
	254	7	Trace	Trace	-	-	-	Many	Mod	-	-
	255	7	-	-	-	Trace	-	Many	Few	-	-
3f	351	7	-	-	-	Trace	-	Many	Mod	-	-
	352	7	Trace	Trace	-	Trace	-	Many	Mod	-	-
	353	7	-	-	-	-	-	Many	Mod	-	-
	354	7	Trace	Trace	-	-	-	Many	Few	-	-
	355	7	Trace	Trace	-	-	-	Many	Mod	-	-
4f	451	7	-	-	-	Few	-	Many	Many	-	-
	452	7	-	-	-	Trace	-	Mod	Few	-	-
	453	7	-	-	-	Mod	-	Many	Mod	-	-
	454	7	Trace	Trace	-	Trace	-	Many	Mod	-	-
	455	7	-	-	-	-	-	Many	Few	-	-

Individual Animal Clinical Pathology Data

Group	Animal	Day	HJB	SM	TOX	DB	VC	BC	PCE	GP	BP
Sex	Number	Number									
1f	151	7	-	-	-	-	-	-	UTD	-	-
	152	7	-	-	-	-	-	-	-	-	-
	153	7	-	-	-	-	-	-	-	-	-
	154	7	-	-	-	-	-	-	-	-	-
	155	7	-	-	-	-	-	-	Adeq	Trace	-
2f	251	7	-	-	-	-	-	-	-	-	-
	252	7	-	-	-	-	-	-	Decr	-	-
	253	7	-	-	-	-	-	-	Adeq	Trace	-
	254	7	-	-	-	-	-	-	Adeq	-	-
	255	7	-	-	-	-	-	-	Adeq	-	-
3f	351	7	-	-	-	-	-	-	Adeq	-	-
	352	7	-	-	-	-	-	-	Adeq	Trace	-
	353	7	-	-	-	-	-	-	UTD	-	-
	354	7	Trace	-	-	-	-	-	Adeq	-	-
	355	7	-	-	-	-	-	-	-	-	-
4f	451	7	Trace	-	-	-	-	-	-	-	-
	452	7	-	-	-	-	-	-	-	-	-
	453	7	Trace	-	-	-	-	-	-	Trace	-
	454	7	Trace	-	-	-	-	-	-	Trace	-
	455	7	-	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Group	Animal Sex Number	Day Number	HEM	LIP	ICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL
1m	101	7	None	None	None	76	25	21.1	342	0.12	10	0.32	71
	102	7	None	None	None	100	31	10.0	245	0.13	12	0.32	79
	103	7	None	None	None	70	23	20.2	267	0.14	10	0.33	74
	104	7	None	None	None	85	26	13.8	166	0.11	11	0.32	64
	105	7	None	None	None	64	27	20.5	193	0.14	11	0.30	55
2m	201	7	Trace	None	None	68	25	18.8	243	0.14	12	0.33	39
	202	7	None	None	None	105	38	12.1	400	0.11	10	0.28	50
	203	7	None	None	None	87	23	19.2	256	0.08	11	0.28	27
	204	7	None	None	None	79	30	16.6	174	0.11	9	0.26	32
	205	7	None	None	None	65	29	18.0	219	0.09	12	0.32	32
3m	301	7	Trace	None	None	73	26	8.4	272	0.14	13	0.29	49
	302	7	None	None	None	92	35	14.6	289	0.11	14	0.26	39
	303	7	None	None	None	80	27	19.3	286	0.12	14	0.28	25
	304	7	Trace	None	None	98	38	5.4	335	0.14	15	0.29	38
	305	7	None	None	None	71	36	11.2	322	0.13	15	0.32	38
4m	401	7	Small	None	None	112	52	5.6	376	0.14	15	0.24	34
	402	7	None	None	None	109	47	7.1	303	0.17	18	0.30	49
	403	7	Small	None	None	114	48	0.0	278	0.16	13	0.29	43
	404	7	Trace	None	None	103	39	3.9	355	0.16	14	0.29	32
	405	7	None	None	None	102	53	9.5	313	0.13	14	0.24	28
1f	151	7	None	None	None	107	21	6.0	130	0.12	19	0.39	71
	152	7	None	None	None	93	23	6.5	123	0.14	14	0.35	58
	153	7	None	None	None	70	20	17.9	75	0.15	14	0.38	88
	154	7	None	None	None	64	19	22.2	119	0.11	13	0.36	78
	155	7	None	None	None	74	19	15.9	116	0.15	13	0.36	68
2f	251	7	None	None	None	100	24	7.6	169	0.13	13	0.32	60
	252	7	None	None	None	95	25	3.4	93	0.13	12	0.36	59
	253	7	None	None	None	84	21	7.2	103	0.13	13	0.37	65
	254	7	None	None	None	87	18	7.1	136	0.10	12	0.35	50
	255	7	None	None	None	64	22	20.2	102	0.13	12	0.37	61
3f	351	7	None	None	None	83	30	16.5	156	0.14	13	0.36	51
	352	7	None	None	None	89	25	5.4	96	0.11	11	0.30	35
	353	7	None	None	None	87	22	20.6	127	0.11	17	0.38	72
	354	7	None	None	None	83	28	13.7	162	0.11	15	0.36	57
	355	7	None	None	None	66	23	16.3	105	0.12	16	0.37	59
4f	451	7	None	None	None	83	25	11.6	97	0.10	12	0.31	39
	452	7	Trace	None	None	95	35	4.8	120	0.12	12	0.32	56
	453	7	None	None	None	75	25	11.5	86	0.09	11	0.32	62
	454	7	None	None	None	109	30	13.3	101	0.09	14	0.31	46
	455	7	Trace	None	None	112	30	7.2	137	0.10	8	0.26	59

Individual Animal Clinical Pathology Data

Group	Animal	Day	TRIG	GLUC	TP	ALB	GLOB	CALC	IPHS	NA	K	CL
Sex	Number	Number	mg/dL	mg/dL	g/dL	g/dL	g/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L
1m	101	7	84	77	6.1	3.7	2.4	10.6	9.5	147.0	6.00	100.2
	102	7	127	76	5.9	3.4	2.5	10.4	10.1	146.1	6.33	95.5
	103	7	77	78	6.3	3.6	2.7	10.9	9.6	148.1	6.32	100.1
	104	7	61	72	6.1	3.5	2.6	10.7	9.6	145.8	6.07	99.9
	105	7	44	88	5.9	3.5	2.4	10.6	9.2	145.3	5.59	98.2
2m	201	7	33	109	6.3	4.1	2.2	11.0	10.0	144.1	6.15	95.8
	202	7	50	90	6.2	4.0	2.2	10.8	9.6	146.6	6.83	97.2
	203	7	29	78	5.7	3.6	2.1	10.6	9.3	145.0	6.03	97.3
	204	7	33	83	5.4	3.5	1.9	10.3	9.4	145.5	6.42	98.0
	205	7	34	92	5.9	3.7	2.2	10.5	9.1	147.4	6.04	99.9
3m	301	7	35	95	5.6	3.8	1.8	10.1	9.9	145.2	6.37	100.1
	302	7	42	96	5.3	3.4	1.9	10.3	9.6	145.5	6.61	98.1
	303	7	36	104	5.5	3.8	1.7	10.4	9.0	144.9	6.44	100.6
	304	7	24	95	5.1	3.5	1.6	10.0	9.3	147.1	6.25	100.3
	305	7	48	103	5.9	3.9	2.0	10.5	8.5	146.1	6.27	101.1
4m	401	7	29	98	4.5	3.1	1.4	9.6	8.0	142.2	6.12	100.9
	402	7	34	78	4.9	3.3	1.6	9.8	8.8	144.1	6.09	101.3
	403	7	26	96	5.2	3.4	1.8	10.0	8.7	144.2	6.39	101.1
	404	7	32	100	5.1	3.4	1.7	10.1	9.9	145.3	6.76	97.8
	405	7	50	118	4.5	3.1	1.4	9.7	9.0	144.2	5.55	100.2
1f	151	7	52	96	6.4	3.9	2.5	10.3	7.1	144.7	5.39	101.8
	152	7	29	97	6.3	3.7	2.6	9.9	6.3	146.3	5.30	102.0
	153	7	113	88	7.3	4.5	2.8	11.2	7.0	143.7	5.80	98.6
	154	7	47	92	6.9	4.2	2.7	11.0	6.8	145.6	5.43	100.7
	155	7	45	91	6.2	3.8	2.4	10.2	6.7	143.7	5.54	99.7
2f	251	7	44	84	6.2	3.7	2.5	10.0	6.8	145.4	5.25	100.5
	252	7	30	94	6.3	3.7	2.6	10.2	7.9	143.9	6.00	99.7
	253	7	40	84	6.7	4.2	2.5	10.8	8.5	144.2	6.18	104.4
	254	7	30	92	7.0	4.1	2.9	10.3	7.2	144.6	5.22	101.1
	255	7	33	100	6.7	4.1	2.6	10.7	6.9	145.0	5.07	100.9
3f	351	7	35	97	6.3	3.9	2.4	10.1	6.8	144.7	5.93	100.8
	352	7	25	74	5.6	3.6	2.0	9.9	7.7	144.1	5.37	102.4
	353	7	24	91	6.1	3.6	2.5	10.8	8.4	145.4	5.40	104.6
	354	7	39	90	6.3	3.9	2.4	10.2	6.8	147.6	5.62	102.9
	355	7	30	80	6.3	3.9	2.4	10.6	7.3	143.0	5.70	97.4
4f	451	7	36	108	6.0	3.8	2.2	10.1	7.2	144.1	5.49	102.9
	452	7	37	85	5.6	3.8	1.8	10.0	7.0	144.2	5.78	99.6
	453	7	36	110	5.3	3.4	1.9	10.2	8.7	145.0	5.50	101.4
	454	7	34	94	5.7	3.8	1.9	10.1	7.0	144.8	5.54	100.1
	455	7	24	68	5.4	3.3	2.1	9.8	7.8	143.3	5.43	102.8

Appendix E
Summary and Individual Animal Pathology Data

Mean Final Body and Organ Weights from Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
BRAIN	1.973 0.021(5)	1.996 0.068(5)	1.940 0.030(5)	1.918 0.077(5)
HEART	1.212 0.086(5)	1.233 0.086(5)	1.134 0.068(5)	0.988* 0.096(5)
KIDNEYS	2.534 0.107(5)	2.915 0.438(5)	2.690 0.127(5)	2.552 0.178(5)
LIVER	10.991 1.444(5)	15.148* 3.132(5)	17.864* 0.777(5)	15.457* 1.881(5)
SPLEEN	0.687 0.090(5)	0.701 0.114(5)	0.603 0.064(5)	0.642 0.127(5)
TESTES	2.781 0.071(5)	2.772 0.175(5)	2.813 0.206(5)	2.421 1.049(5)
THYMUS	0.639 0.187(5)	0.717 0.200(5)	0.617 0.099(5)	0.551 0.074(5)
FINAL BODY WEIGHT (grams)				
	287.5 4.1(5)	287.4 15.8(5)	284.9 8.9(5)	265.8* 7.1(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
BRAIN/ FINAL BODY * 100	0.686 0.010(5)	0.696 0.049(5)	0.681 0.013(5)	0.722* 0.018(5)
HEART/ FINAL BODY * 100	0.421 0.027(5)	0.429 0.017(5)	0.398 0.028(5)	0.372* 0.035(5)
KIDNEYS/ FINAL BODY * 100	0.881 0.031(5)	1.012* 0.121(5)	0.946 0.071(5)	0.960 0.060(5)
LIVER/ FINAL BODY * 100	3.818 0.463(5)	5.242* 0.841(5)	6.273* 0.315(5)	5.816* 0.709(5)
SPLEEN/ FINAL BODY * 100	0.239 0.033(5)	0.243 0.031(5)	0.212 0.024(5)	0.242 0.049(5)
TESTES/ FINAL BODY * 100	0.967 0.037(5)	0.968 0.094(5)	0.988 0.081(5)	0.911 0.397(5)
THYMUS/ FINAL BODY * 100	0.223 0.068(5)	0.247 0.057(5)	0.216 0.035(5)	0.207 0.028(5)

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)

HEART/ BRAIN * 100	61.430 4.332(5)	61.838 4.676(5)	58.521 4.094(5)	51.438* 3.544(5)
KIDNEYS/ BRAIN * 100	128.450 5.735(5)	146.026 21.816(5)	138.766 8.330(5)	132.980 5.494(5)
LIVER/ BRAIN * 100	557.139 73.755(5)	761.435* 170.426(5)	921.173* 42.150(5)	805.185* 85.825(5)
SPLEEN/ BRAIN * 100	34.866 4.773(5)	35.088 5.578(5)	31.129 3.586(5)	33.473 6.334(5)
TESTES/ BRAIN * 100	140.950 4.051(5)	139.058 10.789(5)	145.090 11.767(5)	125.602 54.277(5)
THYMUS/ BRAIN * 100	32.421 9.609(5)	36.072 10.739(5)	31.797 5.184(5)	28.745 4.168(5)

Data arranged as: Mean
 Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.

@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

Mean Final Body and Organ Weights from Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 300 mg/kg/day	Group 4 1000 mg/kg/day
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
BRAIN	1.879 0.044(5)	1.849 0.050(5)	1.845 0.060(5)	1.846 0.055(5)
HEART	0.842 0.070(5)	1.205 0.769(5)	0.827 0.059(5)	0.799 0.030(5)
KIDNEYS	1.611 0.064(5)	1.792 0.186(5)	1.710 0.100(5)	1.854* 0.117(5)
LIVER	6.536 0.367(5)	6.679 0.602(5)	6.497 0.682(5)	8.127* 0.713(5)
SPLEEN	0.478 0.090(5)	0.473 0.014(5)	0.479 0.067(5)	0.437 0.052(5)
THYMUS	0.478 0.095(5)	0.516 0.066(5)	0.458 0.151(5)	0.447 0.098(5)
FINAL BODY WEIGHT (grams)				
	185.9 6.9(5)	192.3 11.0(5)	192.2 9.0(5)	192.7 10.0(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
BRAIN/ FINAL BODY * 100	1.012 0.037(5)	0.963 0.041(5)	0.961 0.049(5)	0.960 0.061(5)
HEART/ FINAL BODY * 100	0.454 0.039(5)	0.646 0.466(5)	0.431 0.032(5)	0.415 0.008(5)
KIDNEYS/ FINAL BODY * 100	0.868 0.060(5)	0.932 0.079(5)	0.890 0.043(5)	0.963 0.064(5)
LIVER/ FINAL BODY * 100	3.517 0.170(5)	3.469 0.152(5)	3.378 0.260(5)	4.229* 0.450(5)
SPLEEN/ FINAL BODY * 100	0.259 0.057(5)	0.246 0.012(5)	0.249 0.028(5)	0.227 0.032(5)
THYMUS/ FINAL BODY * 100	0.256 0.044(5)	0.269 0.032(5)	0.237 0.074(5)	0.231 0.048(5)
MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)				
HEART/ BRAIN * 100	44.872 4.355(5)	66.012 44.521(5)	44.859 3.288(5)	43.289 1.949(5)

KIDNEYS/ BRAIN * 100	85.739 3.810(5)	96.795* 7.889(5)	92.755 5.781(5)	100.552* 7.920(5)
LIVER/ BRAIN * 100	348.073 23.563(5)	360.927 26.217(5)	351.980 32.524(5)	440.752* 44.231(5)
SPLEEN/ BRAIN * 100	25.464 4.813(5)	25.588 0.998(5)	25.904 3.165(5)	23.736 3.546(5)
THYMUS/ BRAIN * 100	25.402 4.807(5)	27.887 3.008(5)	24.824 8.149(5)	24.346 5.821(5)

Data arranged as: Mean
 Standard deviation (Number of values included in calculation)

- * Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
- @ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Bodywt g	Brain g	Heart g	Kidneys g	Liver g	Spleen g	Testes g	Thymus g
1m	101	288.1	1.965	1.310	2.686	12.632	0.789	2.798	0.545
	102	290.5	1.954	1.167	2.576	11.748	0.634	2.741	0.461
	103	292.1	1.999	1.294	2.532	11.597	0.646	2.683	0.657
	104	281.9	1.955	1.179	2.404	9.173	0.777	2.814	0.949
	105	285.1	1.992	1.110	2.472	9.806	0.591	2.867	0.585
	Mean	287.54	1.9730	1.2120	2.5340	10.9912	0.6874	2.7806	0.6394
S.D.	4.11	0.0211	0.0864	0.1068	1.4442	0.0897	0.0707	0.1870	
N	5	5	5	5	5	5	5	5	
2m	201	298.4	1.976	1.235	2.841	19.147	0.749	2.878	0.733
	202	304.8	1.931	1.299	3.406	17.843	0.757	2.587	1.029
	203	289.3	2.028	1.324	2.876	13.457	0.780	2.906	0.716
	204	279.6	2.098	1.201	3.198	13.197	0.716	2.575	0.622
	205	264.8	1.946	1.107	2.252	12.096	0.501	2.912	0.487
	Mean	287.38	1.9958	1.2332	2.9146	15.1480	0.7006	2.7716	0.7174
S.D.	15.80	0.0681	0.0859	0.4381	3.1319	0.1139	0.1745	0.1997	
N	5	5	5	5	5	5	5	5	
3m	301	287.4	1.924	1.243	2.622	18.633	0.688	2.920	0.619
	302	276.5	1.910	1.125	2.870	16.684	0.650	3.076	0.742
	303	276.8	1.923	1.145	2.777	18.450	0.547	2.645	0.467
	304	285.8	1.960	1.061	2.578	17.967	0.585	2.569	0.609
	305	298.2	1.981	1.098	2.602	17.587	0.546	2.853	0.646
	Mean	284.94	1.9396	1.1344	2.6898	17.8642	0.6032	2.8126	0.6166
S.D.	8.95	0.0297	0.0684	0.1274	0.7769	0.0635	0.2061	0.0988	
N	5	5	5	5	5	5	5	5	
4m	401	276.0	2.045	1.107	2.820	16.533	0.727	2.766	0.575
	402	264.7	1.849	0.877	2.402	14.769	0.662	0.550	0.660
	403	269.4	1.917	0.929	2.394	15.166	0.454	2.890	0.493
	404	259.6	1.863	0.959	2.517	12.915	0.590	2.942	0.472
	405	259.3	1.916	1.067	2.627	17.902	0.779	2.957	0.553
	Mean	265.80	1.9180	0.9878	2.5520	15.4570	0.6424	2.4210	0.5506
S.D.	7.05	0.0773	0.0962	0.1776	1.8812	0.1269	1.0486	0.0743	
N	5	5	5	5	5	5	5	5	

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Individual Animal Final Body and Organ Weights

Group	Animal	Brain	Heart	Kidney	Liver	Spleen	Testes	Thymus
Sex	Number	%FBW						
1m	101	0.6821	0.4547	0.9323	4.3846	0.2739	0.9712	0.1892
	102	0.6726	0.4017	0.8867	4.0441	0.2182	0.9435	0.1587
	103	0.6844	0.4430	0.8668	3.9702	0.2212	0.9185	0.2249
	104	0.6935	0.4182	0.8528	3.2540	0.2756	0.9982	0.3366
	105	0.6987	0.3893	0.8671	3.4395	0.2073	1.0056	0.2052
	Mean	0.68626	0.42138	0.88114	3.81848	0.23924	0.96740	0.22292
	S.D.	0.01018	0.02741	0.03104	0.46278	0.03283	0.03669	0.06801
N	5	5	5	5	5	5	5	
2m	201	0.6622	0.4139	0.9521	6.4166	0.2510	0.9645	0.2456
	202	0.6335	0.4262	1.1175	5.8540	0.2484	0.8488	0.3376
	203	0.7010	0.4577	0.9941	4.6516	0.2696	1.0045	0.2475
	204	0.7504	0.4295	1.1438	4.7200	0.2561	0.9210	0.2225
	205	0.7349	0.4181	0.8505	4.5680	0.1892	1.0997	0.1839
	Mean	0.69640	0.42908	1.01160	5.24204	0.24286	0.96770	0.24742
	S.D.	0.04885	0.01717	0.12092	0.84106	0.03109	0.09368	0.05655
N	5	5	5	5	5	5	5	
3m	301	0.6695	0.4325	0.9123	6.4833	0.2394	1.0160	0.2154
	302	0.6908	0.4069	1.0380	6.0340	0.2351	1.1125	0.2684
	303	0.6947	0.4137	1.0033	6.6655	0.1976	0.9556	0.1687
	304	0.6858	0.3712	0.9020	6.2866	0.2047	0.8989	0.2131
	305	0.6643	0.3682	0.8726	5.8977	0.1831	0.9567	0.2166
	Mean	0.68102	0.39850	0.94564	6.27342	0.21198	0.98794	0.21644
	S.D.	0.01340	0.02793	0.07107	0.31482	0.02439	0.08101	0.03532
N	5	5	5	5	5	5	5	
4m	401	0.7409	0.4011	1.0217	5.9902	0.2634	1.0022	0.2083
	402	0.6985	0.3313	0.9074	5.5795	0.2501	0.2078	0.2493
	403	0.7116	0.3448	0.8886	5.6295	0.1685	1.0728	0.1830
	404	0.7176	0.3694	0.9696	4.9750	0.2273	1.1333	0.1818
	405	0.7389	0.4115	1.0131	6.9040	0.3004	1.1404	0.2133
	Mean	0.72150	0.37162	0.96008	5.81564	0.24194	0.91130	0.20714
	S.D.	0.01818	0.03468	0.06038	0.70924	0.04887	0.39719	0.02758
N	5	5	5	5	5	5	5	

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Individual Animal Final Body and Organ Weights

Group	Animal	Heart	Kidney	Liver	Spleen	Testes	Thymus
Sex	Number	%Brain	%Brain	%Brain	%Brain	%Brain	%Brain
1m	101	66.6667	136.6921	642.8499	40.1527	142.3919	27.7354
	102	59.7236	131.8321	601.2282	32.4463	140.2764	23.5926
	103	64.7324	126.6633	580.1401	32.3162	134.2171	32.8664
	104	60.3069	122.9668	469.2072	39.7442	143.9386	48.5422
	105	55.7229	124.0964	492.2691	29.6687	143.9257	29.3675
	Mean	61.43050	128.45014	557.13890	34.86562	140.94994	32.42082
	S.D.	4.33223	5.73547	73.75529	4.77269	4.05127	9.60873
N	5	5	5	5	5	5	
2m	201	62.5000	143.7753	968.9777	37.9049	145.6478	37.0951
	202	67.2708	176.3853	924.0290	39.2025	133.9720	53.2885
	203	65.2860	141.8146	663.5602	38.4615	143.2939	35.3057
	204	57.2450	152.4309	629.0276	34.1277	122.7359	29.6473
	205	56.8859	115.7246	621.5827	25.7451	149.6403	25.0257
	Mean	61.83754	146.02614	761.43544	35.08834	139.05798	36.07246
	S.D.	4.67603	21.81563	170.42641	5.57800	10.78925	10.73941
N	5	5	5	5	5	5	
3m	301	64.6050	136.2786	968.4511	35.7588	151.7672	32.1726
	302	58.9005	150.2618	873.5079	34.0314	161.0471	38.8482
	303	59.5424	144.4098	959.4384	28.4451	137.5455	24.2850
	304	54.1327	131.5306	916.6837	29.8469	131.0714	31.0714
	305	55.4266	131.3478	887.7839	27.5618	144.0182	32.6098
	Mean	58.52144	138.76572	921.17300	31.12880	145.08988	31.79740
	S.D.	4.09374	8.33027	42.14975	3.58577	11.76651	5.18357
N	5	5	5	5	5	5	
4m	401	54.1320	137.8973	808.4597	35.5501	135.2567	28.1174
	402	47.4310	129.9081	798.7561	35.8031	29.7458	35.6950
	403	48.4611	124.8826	791.1320	23.6828	150.7564	25.7173
	404	51.4761	135.1047	693.2367	31.6694	157.9173	25.3355
	405	55.6889	137.1086	934.3424	40.6576	154.3319	28.8622
	Mean	51.43782	132.98026	805.18538	33.47260	125.60162	28.74548
	S.D.	3.54426	5.49418	85.82482	6.33370	54.27719	4.16839
N	5	5	5	5	5	5	

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Bodywt g	Brain g	Heart g	Kidneys g	Liver g	Spleen g	Thymus g
1f	151	185.1	1.858	0.941	1.674	6.882	0.411	0.406
	152	176.1	1.828	0.817	1.618	6.246	0.584	0.391
	153	193.6	1.862	0.886	1.545	6.989	0.402	0.521
	154	191.3	1.910	0.767	1.545	6.262	0.427	0.623
	155	183.2	1.938	0.800	1.671	6.300	0.568	0.449
	Mean	185.86	1.8792	0.8422	1.6106	6.5358	0.4784	0.4780
	S.D.	6.94	0.0441	0.0703	0.0639	0.3674	0.0897	0.0955
	N	5	5	5	5	5	5	5
2f	251	200.3	1.881	0.860	1.837	6.853	0.473	0.570
	252	193.7	1.843	0.783	1.642	6.590	0.491	0.445
	253	174.2	1.771	2.577	1.573	5.706	0.461	0.467
	254	191.6	1.902	0.882	2.035	6.939	0.458	0.600
	255	201.6	1.847	0.923	1.873	7.309	0.481	0.500
	Mean	192.28	1.8488	1.2050	1.7920	6.6794	0.4728	0.5164
	S.D.	10.96	0.0499	0.7687	0.1858	0.6020	0.0138	0.0665
	N	5	5	5	5	5	5	5
3f	351	190.2	1.752	0.822	1.687	6.449	0.416	0.382
	352	197.6	1.826	0.833	1.757	5.953	0.510	0.653
	353	182.8	1.862	0.734	1.749	6.099	0.401	0.252
	354	185.5	1.876	0.897	1.549	6.315	0.509	0.523
	355	204.8	1.909	0.850	1.809	7.667	0.557	0.480
	Mean	192.18	1.8450	0.8272	1.7102	6.4966	0.4786	0.4580
	S.D.	9.02	0.0599	0.0595	0.1000	0.6817	0.0671	0.1508
	N	5	5	5	5	5	5	5
4f	451	190.9	1.832	0.787	2.004	9.355	0.448	0.459
	452	196.9	1.885	0.825	1.723	7.945	0.407	0.480
	453	188.0	1.765	0.780	1.827	8.070	0.523	0.540
	454	180.5	1.907	0.766	1.774	7.673	0.401	0.281
	455	207.2	1.843	0.836	1.943	7.594	0.405	0.477
	Mean	192.70	1.8464	0.7988	1.8542	8.1274	0.4368	0.4474
	S.D.	10.03	0.0548	0.0302	0.1170	0.7132	0.0518	0.0979
	N	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Brain %FBW	Heart %FBW	Kidney %FBW	Liver %FBW	Spleen %FBW	Thymus %FBW
1f	151	1.0038	0.5084	0.9044	3.7180	0.2220	0.2193
	152	1.0380	0.4639	0.9188	3.5468	0.3316	0.2220
	153	0.9618	0.4576	0.7980	3.6100	0.2076	0.2691
	154	0.9984	0.4009	0.8076	3.2734	0.2232	0.3257
	155	1.0579	0.4367	0.9121	3.4389	0.3100	0.2451
	Mean	1.01198	0.45350	0.86818	3.51742	0.25888	0.25624
	S.D.	0.03727	0.03933	0.06000	0.16984	0.05737	0.04374
	N	5	5	5	5	5	5
2f	251	0.9391	0.4294	0.9171	3.4214	0.2361	0.2846
	252	0.9515	0.4042	0.8477	3.4022	0.2535	0.2297
	253	1.0166	1.4793	0.9030	3.2755	0.2646	0.2681
	254	0.9927	0.4603	1.0621	3.6216	0.2390	0.3132
	255	0.9162	0.4578	0.9291	3.6255	0.2386	0.2480
	Mean	0.96322	0.64620	0.93180	3.46924	0.24636	0.26872
	S.D.	0.04077	0.46628	0.07922	0.15162	0.01228	0.03234
	N	5	5	5	5	5	5
3f	351	0.9211	0.4322	0.8870	3.3906	0.2187	0.2008
	352	0.9241	0.4216	0.8892	3.0127	0.2581	0.3305
	353	1.0186	0.4015	0.9568	3.3364	0.2194	0.1379
	354	1.0113	0.4836	0.8350	3.4043	0.2744	0.2819
	355	0.9321	0.4150	0.8833	3.7437	0.2720	0.2344
	Mean	0.96144	0.43078	0.89026	3.37754	0.24852	0.23710
	S.D.	0.04908	0.03155	0.04342	0.25969	0.02761	0.07399
	N	5	5	5	5	5	5
4f	451	0.9597	0.4123	1.0498	4.9005	0.2347	0.2404
	452	0.9573	0.4190	0.8751	4.0350	0.2067	0.2438
	453	0.9388	0.4149	0.9718	4.2926	0.2782	0.2872
	454	1.0565	0.4244	0.9828	4.2510	0.2222	0.1557
	455	0.8895	0.4035	0.9377	3.6651	0.1955	0.2302
	Mean	0.96036	0.41482	0.96344	4.22884	0.22746	0.23146
	S.D.	0.06070	0.00781	0.06397	0.45029	0.03204	0.04765
	N	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Heart %Brain	Kidney %Brain	Liver %Brain	Spleen %Brain	Thymus %Brain
1f	151	50.6459	90.0969	370.3983	22.1206	21.8515
	152	44.6937	88.5120	341.6849	31.9475	21.3895
	153	47.5832	82.9753	375.3491	21.5897	27.9807
	154	40.1571	80.8901	327.8534	22.3560	32.6178
	155	41.2797	86.2229	325.0774	29.3086	23.1682
	Mean	44.87192	85.73944	348.07262	25.46448	25.40154
	S.D.	4.35475	3.81001	23.56291	4.81313	4.80660
	N	5	5	5	5	5
2f	251	45.7204	97.6608	364.3275	25.1462	30.3030
	252	42.4851	89.0939	357.5692	26.6413	24.1454
	253	145.5110	88.8199	322.1909	26.0305	26.3693
	254	46.3722	106.9926	364.8265	24.0799	31.5457
	255	49.9729	101.4077	395.7228	26.0422	27.0709
	Mean	66.01232	96.79498	360.92738	25.58802	27.88686
	S.D.	44.52058	7.88871	26.21678	0.99763	3.00800
	N	5	5	5	5	5
3f	351	46.9178	96.2900	368.0936	23.7443	21.8037
	352	45.6188	96.2212	326.0131	27.9299	35.7612
	353	39.4200	93.9313	327.5510	21.5360	13.5338
	354	47.8145	82.5693	336.6205	27.1322	27.8785
	355	44.5259	94.7617	401.6239	29.1776	25.1441
	Mean	44.85940	92.75470	351.98042	25.90400	24.82426
	S.D.	3.28803	5.78078	32.52359	3.16516	8.14932
	N	5	5	5	5	5
4f	451	42.9585	109.3886	510.6441	24.4541	25.0546
	452	43.7666	91.4058	421.4854	21.5915	25.4642
	453	44.1926	103.5127	457.2238	29.6317	30.5949
	454	40.1678	93.0257	402.3597	21.0278	14.7352
	455	45.3608	105.4259	412.0456	21.9750	25.8817
	Mean	43.28926	100.55174	440.75172	23.73602	24.34612
	S.D.	1.94859	7.91998	44.23080	3.54645	5.82081
	N	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix F
Individual Mechanistic Evaluation Data

Peroxisomal Beta-Oxidation Activity in 7-Day Male Rats

Animal Number	Group	Dosage (mg/kg)	Rate (nmol/mg-min)	Group Average	Standard Deviation	
101	1	0	6.6	6.3	0.7	
102	1	0	5.2			
103	1	0	6.4			
104	1	0	7.1			
105	1	0	6.1			
201	2	30	60.7	43.8	10.0	*
202	2	30	43.0			
203	2	30	37.4			
204	2	30	35.1			
205	2	30	42.9			
301	3	300	55.4	62.1	6.6	*
302	3	300	67.8			
303	3	300	54.3			
304	3	300	66.9			
305	3	300	66.0			
401	4	1000	61.1	65.5	8.9	*
402	4	1000	80.6			
403	4	1000	65.6			
404	4	1000	62.2			
405	4	1000	57.8			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.

Peroxisomal Beta-Oxidation Activity in 7-Day Female Rats

Animal Number	Group	Dosage (mg/kg)	Rate (nmol/mg-min)	Group Average	Standard Deviation	
151	1	0	5.8	5.3	0.7	
152	1	0	4.2			
153	1	0	5.4			
154	1	0	5.8			
155	1	0	5.1			
251	2	30	4.8	5.7	1.2	
252	2	30	7.4			
253	2	30	6.3			
254	2	30	5.1			
255	2	30	4.7			
351	3	300	11.2	11.1	1.2	
352	3	300	11.1			
353	3	300	12.7			
354	3	300	9.4			
355	3	300	11.1			
451	4	1000	34.0	28.7	9.1	@
452	4	1000	33.1			
453	4	1000	30.7			
454	4	1000	33.2			
455	4	1000	12.5			

@ Statistically significant difference from control ($p \leq 0.05$) by Dunn's test.

Microsomal Cytochrome P-450 Content in 7-Day Male Rats

Animal Number	Group	Dosage (mg/kg)	nmol/mg protein	Group Average	Standard Deviation	
101	1	0	0.331	0.503	0.171	
102	1	0	0.421			
103	1	0	0.465			
104	1	0	0.515			
105	1	0	0.783			
201	2	30	0.606	0.612	0.059	
202	2	30	0.602			
203	2	30	0.608			
204	2	30	0.539			
205	2	30	0.704			
301	3	300	0.820	0.848	0.121	*
302	3	300	0.764			
303	3	300	0.945			
304	3	300	0.999			
305	3	300	0.713			
401	4	1000	0.858	0.913	0.207	*
402	4	1000	0.855			
403	4	1000	0.626			
404	4	1000	1.152			
405	4	1000	1.073			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.

Microsomal Cytochrome P-450 Content in Female Rats

Animal Number	Group	Dosage (mg/kg)	nmol/mg protein	Group Average	Standard Deviation	
151	1	0	0.452	0.402	0.072	
152	1	0	0.450			
153	1	0	0.455			
154	1	0	0.358			
155	1	0	0.295			
251	2	30	0.411	0.383	0.039	
252	2	30	0.425			
253	2	30	0.378			
254	2	30	0.374			
255	2	30	0.325			
351	3	300	0.442	0.419	0.047	
352	3	300	0.474			
353	3	300	0.379			
354	3	300	0.439			
355	3	300	0.363			
451	4	1000	0.551	0.493	0.045	*
452	4	1000	0.529			
453	4	1000	0.471			
454	4	1000	0.465			
455	4	1000	0.447			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.